# Experimental Studies on Attitude of Dogs with Regenerated Liver Against Hemorrhagic Shock

by

MASAHIKO TSUJI

2nd Department of Surgery Kanazawa University, Medical School
(Director: Prof. Dr. ICHIO HONJO)
Received for Publication July 31, 1965

**CONTENT**

I. Introduction
II. Materials and Methods
1. Materials
2. Production of Hemorrhagic Shock
i. Wiggers' Method (Western Reserve Method)
ii. Modified Method of Lamson
3. Examinations and Methods
i. Maximum Bleeding Volume
ii. Time-span to Maximum Bleeding Volume, Spontaneous Returning Time and Time-span to 15 and 30 per cent Spontaneous Returning
iii. Survival Time
iv. Changes in Portal Pressure
v. Changes in Hematocrit Ratio
vi. Histological Studies
III. Results
1. Results in Animals with 50 per cent Liver Resection
i. Change in Red Blood Cell Count
ii. Rate of Hepatic Regeneration
2. Results of Experiments with Wigger's Method
i. Maximum Bleeding Volume
ii. Survival Rate
3. Results of Experiments with Modified Method of Lamson
i. Group of Blood Returning at the Time of 15 per cent Spontaneous Returning
ii. Group of Blood Returning at the Time of 30 per cent Spontaneous Returning
a. Maximum Bleeding Volume
b. Time-span to Maximum Bleeding Volume
c. Time-span to Spontaneous Returning
d. Time-span to 30 per cent Spontaneous Returning
e. Survival Rate
f. Influence of Sex on the Results
g. Relation to Temperature
4. Changes in Portal Pressure
5. Changes in Hematocrit Ratio
6. Histological Findings
i. Before Withdrawal of Blood
ii. At the Time of Spontaneous Returning
iii. At the Time of 30 per cent Spontaneous Returning
iv. At the Time of 70 per cent Spontaneous Returning
IV. Discussion
V. Summary
VI. References

## I. INTRODUCTION

It is well known fact that the liver plays an important role against various surgical intervention. Above all, significance of the liver in hemorrhagic shock includes numerous problems attracting interests of surgeons in every respect.

Hepatic resection has been considered to be a principal treatment for surgical diseases of the liver since early days, and many reports on this aspect can be seen[28)44)]. As the

* The gist of the present paper was reported at 51st Annual Meeting of Japanesee Soiety of the Diseases of Digestive Organs.

marvellous understanding and advancement of physiology[23)31)], anatomy[32)] and hepatic regeneration[14)38)] have come to be introduced to the operative techniques, together with the advancement in anesthesiology, extensive hepatic resection is positively carried out today not only for primary malignant neoplasms of the liver[25)35)47)], but for metastatic carcinoma of the liver as concomitant removal of the malignant involvement. Accordingly, cases of hepatic resection are rapidly increasing in number at present, attracting attention of clinicians to pathophysiology in organism with regenerated liver.

Notwithstanding the residual liver parenchyma encounters serious disturbances in intrahepatic circulation, in liver function and in enzymatic system of the liver, showing degeneration of liver cells after hepatic resection, the residual liver parenchyma well stands against this aggression and comes to exceed preoperative weight several weeks after surgery[2)7)24)27)34)36)]. On the other hand, however, so-called liver death, as pointed out be HYED[26)], BOYCE and others[8)], implies an extremely delicate aspect of the liver against aggressions in some occasions. It is also well noticed that resistance against aggressions is smaller in organisms with impaired liver[12)18)].

Pathophysiology of the liver in hemorrhagic shock has been investigated by WIGGERS[49)], FINE[13)], SHORR[42)] and others from various aspects, and prevailing opinions attribute the cause of experimental hemorrhagic irreversible shock to liver anoxia. As decribed in the above, the residual liver parenchyma well stands against the temporary serious liver insufficiency following hepatic resection and regenerates remarkably to restore to normal liver in its weight, size and histological findings. When an organism with thus regenerated liver encounters hemorrhagic shock which leads to profound liver anoxia, it is an interesting clinical problem to clarify whether this organism shows tolerance by the phenomenon of familiarization to aggression, as pointed out by PAREIS and others[37)], or it is less resistant as organisms having the impaired liver.

In the present experiment, the attitude of regenerated liver against hemorrhagic shock was studied from such a standpoint, in order to explore an aspect of pathophysiology of regenerated liver.

## II. MATERIALS AND METHODS

1. Materials

Seventy-two adult mongrel healthy dogs of both sexes weighing from 7.5 to 13.0 kg were used in the present experiment after they were observed at shortest for 3 days feeding with mixed food. Experimental animals were divided into control dogs and those with regenerated liver.

i) First Group ; Group of normal dogs for control study.

ii) Second Group ; Group of dogs with regenerated liver.

Fifty per cent of the entire liver was first resected and the dogs were subjected to experiment 2 months after surgery. Dogs were fixed in the spine position on the table and the abdomen was opened with upper median incision under intravenous anesthesia with 25 mg/kg body weight of pentothal sodium. The liver hilus was adequately exposed. Then, the entire left superior, and entire left inferior lobes of the liver were resected by mass ligature, and partial resection of the quadrate lobe and middle lobe was additionally performed. After the resection of the liver, the abdomen was closed. The dogs were subjected to observation for 2 months, and the animals looked healthy were used as those with regenerated liver. Hepatic resection was carried out so that the weight of resected liver might correspond to 50 per cent of the entire liver weight. The entire liver weight was assumed to be 3.0 per cent of the body weight according to the result of KAMIMURA, in our clinic.

2. Production of Hemorrahgic Shock

Both control and experimental dogs kept away from diet for about 1 to 2 hours on the very day of the experiment. As shown in Fig. 1, the dogs were fixed in the spine position and anesthetized with intravenous injection of 15 to 25 mg/kg body weight of pentothal sodium. A polyethylene catheter of 3 mm in diameter was inserted into the femoral artery, and 3 mg/kg body weight of heparin sodium was administered. A three-way-cock was connected to irrigator and mercurial manometer for artificial bleeding, returning of blood and determination of arterial pressure, and another three-way-cock was used for returning of blood and other purposes. All the apparatus used in the experiment were strictly sterilized and all the experimental procedures were carried out in aseptic condition.

i) WIGGERS' Method (Western Reserve Method)[49]

Blood was rapidly withdrawn through the polyethylene catheter inserted into the femoral artery. As shown in Fig. 2, when the average arterial pressure reached 50 mmHg, arterial presaure was maintained in that level for 90 minutes. Then, blood was further withdrawn and arterial pressure was held in a level of 30 mmHg for 45 minutes, and entire withdrawn blood was returned.

ii) Modified Method of LAMSON[29]

From the catheter inserted into the femoral artery, blood was withdrawn into an

**Fig. 1** Illustration of Experiment. Position and Direction of Catheter

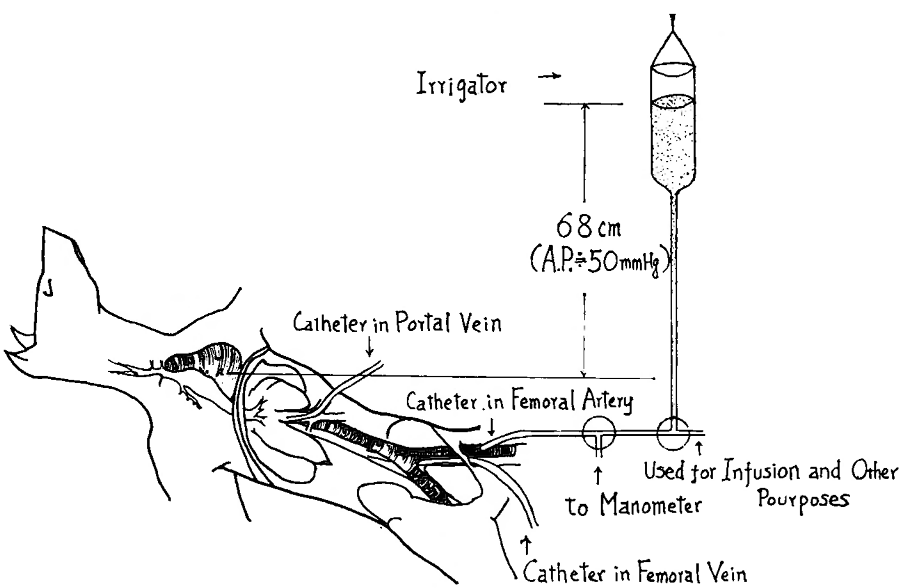
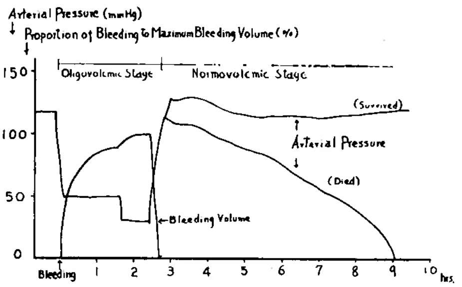


**Fig. 2** Changes of Arterial Pressure and Bleeding Volume in Hemorrhagic Shock by Wiggers' Method




irrigator which was kept in the height of 68 cm from the heart of the animal fixed in the spine position. As shown in Fig. 3, by shifting the irrigator up and down, arterial pressure was held in a level of 50 mmHg, and the entire withdrawn blood was returned after certain interval of time.

3. Examinations and Methods

In WIGGERS' method, maximum bleeding volume and survival time were determined both in control and experimental animals, and in LAMSON's method, maximum bleeding volume, time-span to maximum bleeding volume, spontaneous returning time and survival time were determined. Portal pressure and hematocrit ratio were determined to disclose an aspect of intrahepatic circulation and hemodynamics, and changes in intrahepatic circulation and liver cells were studied histologically.

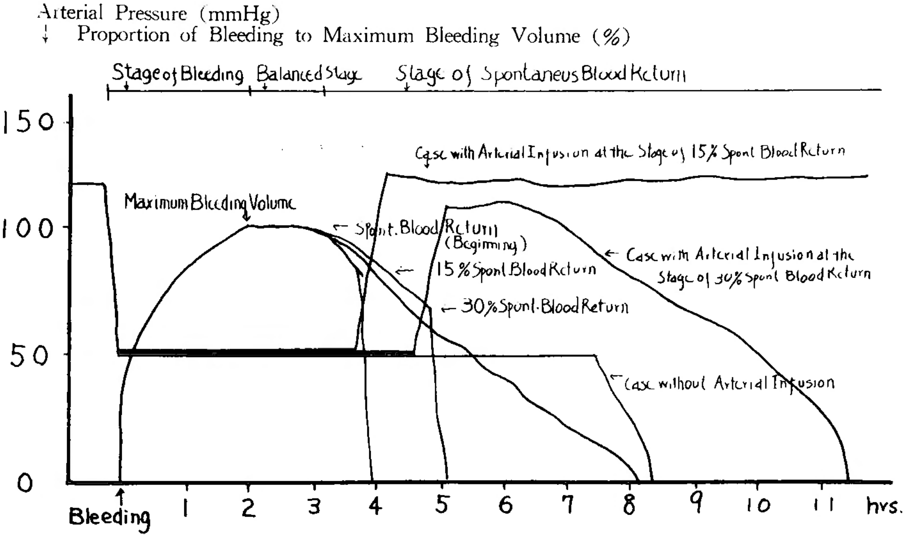
i) Maximum Bleeing Volume

When WIGGERS' method is used, the term of maximum bleeding volume represents the volume of bleeding at a moment in which withdrawn blood volume required for the production of shock state was the largest, while in modified LAMSON's method it means the volume of bleeding at a moment in which increment of bleeding ceases. Fluctuation of bleeding volume was represented in a unit of 10 cc and determination was performed every 10 minutes.

ii) Time-span to maximum bleeding volume, spontaneous returning time and time-span to 15 and 30 per cent spontaneous returning.

As bleeding is commenced using modified method of LAMSON, volume of blood within

**Fig. 3** Changes of Arterial Pressure and Bleeding Volume in Hemorrhagic Shock by Modified Method of Lamson



the irrigator continues to increase, which ceases, however, after certain interval of time. The interval of time between the commencement of bleeding and this moment is defined as time-span to maximum bleeding volume. Volume of bleeding does not change for a while thereafter (this is called balanced stage), and it begins to decrease after certain interval of time. This moment is called spontaneous returning time. Blood within the irrigator continues to decrease thereafter, the moment, in which already returned blood volume reaches 15 or 30 per cent of the maximum bleeding volume, is called time-span to 15 or 30 per cent spontaneous returning, respectively.

Time-span to maximum bleeding volume corresponds to the time required for decreasing blood pressure to 50 mmHg, and spontaneous returning time corresponds to the moment in which the compensatory capacity of organism comes to be unable to maintain blood pressure of 50 mmHg. As mentioned in the below, time-span to 15 and 30 per cent spontaneous returning is considered to correspond to an adequate interval of time to produce reversible and irreversible shock, respectively. In the present experiment, it was intended to find out some differences between control and experimental dogs, from the difference of these intervals of time. Reading of these time was considerably difficult, and it was done by the help of movement of small air-bubble in the catheter placed in a horizontal plane, which was watched for a while. During the experiment, obstruction was frequently observed due to blood clotting, but it was removed by additional administration of heparin, aspiration and/or pushing with syringe.

iii) Survival time

Interval of time between the commencement of bleeding and death was checked. When animals survived over 12 hours, observation was done thereafter every 1 hour, and in the survivals of more than 18 hours, it was pursued if the animals were alive or dead.

iv) Changes in portal pressure

Hemorrhagic shock was produced in 5 control and 5 experimental dogs using modified method of Lamson. The entire blood within the irrigator was returned at 30 per cent spontaneous returning stage, and portal pressure was simultaneously determined. Portal pressure was determined through the catheter inserted into the portal vein from a branch of mesenteric vein by laparotomy prior to the production of shock state.

v) Changes in hematocrit ratio

Hemorrhagic shock was produced by modified method of Lamson in 6 control and 6 experimental dogs. Hematocrit ratio, was determined at the moments of maximum bleeding, spontaneous returning time, time of 30 per cent spontaneous returning and 90 minutes after returning of the entire withdrawn blood. Determination of hematocrit ratio was done following the method of Wintrobe using blood taken from the femoral artery.

vi) Histological Studies

Histological study was carried out 1 control and 1 experimental dogs. The animals were anesthetized as described in the above, and the abdomen was opened with upper median incision. Tissue section of the liver was taken from the marginal part of the hepatic lobe. The sections were also taken from a dog subjected to the Lamson's method without blood return, at the time of spontaneous returning, time of 30 and 70 per cent spontaneous returning of the withdrawn blood. The sections taken from the liver were immediately fixed in 10 per cent formalin, which were provided for production of paraffin section. The microscopic sections were stained with eosin and hematoxylin.

## III. RESULTS

1. Results in Animals with 50 per cent Liver Resection

i. Change in red blood cell count

As shown in Tab. 1, red blood cell count was $434\times10^4\pm16\times10^4$, on the average, 1 week after hepatic resection, revealing a decrease of 15 per cent compared to preoperative level of $514\times10^4\pm33\times10^4$. Red blood cell count remained in a low level of $480\times10^4\pm21\times10^4$, even 4 weeks after surgery, which, however, roughly restored to preoperative level to become $514\times10^4\pm35\times10^4$, 8 weeks after surgery.

ii. Rate of hepatic regeneration

As represented in Tab. 2, rate of hepatic regeneration was from 86 to 111 per cent, $97\pm8$ per cent on the average, of the preoperative entire liver weight, which corresponded to 71 to 122 per cent, $94\pm16$ per cent on the average, of the resected liver weight, 2 months after hepatic resection.

2. Results of Experiments with WIGGERS' Method

Experiments of hemorrhagic shock following WIGGERS' method was carried out in 11 control and 9 experimental dogs, during the period from September to December in 1963, as shown in Tab. 3 and Tab. 4.

i. Maximum bleeding volume

As shown in Fig. 4, maximum bleeding volume in control dogs was from 38 to 53 cc/kg body weight, $46\pm3$ cc/kg body weight on the average, showing considerable individual difference. Maximum bleeding volume in experimental dogs was from 41 to 54 cc/kg body weight, $47\pm4$ cc/kg body weight. Although there was not a small individual diference in both of these groups, a significant difference could not be found in these 2 groups.

ii. Survival rate

Twelve hour survival rate in control group was 6/11 (54 per cent), as shown in Tab. 3, and 24 hour survival rate was 2/11 (18 per cent), while 12 hour survival rate in experimental group was 5/9 (55 per cent), as shown in Tab. 4, and 24 hour survival rate was 2/9 (22 per cent), revealing no significant difference in these 2 groups.

3. Results of Experiments with Modified Method of LAMSON

**Tab. 1** Changes of Red Blood Cell Count after 50% Hepatectomy

| Dog No. | Preope. $\times10^4$ | After 1W $\times10^4$ | After 2W $\times10^4$ | After 4W $\times10^4$ | After 6W $\times10^4$ | After 8W $\times10^4$ |
|---|---|---|---|---|---|---|
| 2 | 510 | 426 | 442 | 466 | 500 | 508 |
| 6 | 546 | 438 | 458 | 502 | 551 | 551 |
| 8 | 468 | 412 | 440 | 460 | 456 | 464 |
| 81 | 482 | 421 | 400 | 463 | 472 | 486 |
| 82 | 564 | 468 | 506 | 510 | 526 | 557 |
| Mean | $514\pm33$ | $434\pm16$ | $449\pm27$ | $480\pm21$ | $501\pm30$ | $514\pm35$ |

**Tab. 2** Regeneration of Liver 60 Days after 50% Hepatectomy

| Dog No. | Body Weight kg | | Liver at Operation, Caleulaled | | | Liver Post Mortem | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Reop. | Post Mortem | Removed g | Remnant g | Total g | Total g | Inerement g | Original Liver % | Regeneration % |
| 2 | 9.0 | 9.0 | 136 | 134 | 270 | 260 | 126 | 96 | 93 |
| 6 | 9.0 | 7.5 | 132 | 138 | 270 | 232 | 94 | 86 | 71 |
| 8 | 8.5 | 9.0 | 129 | 126 | 255 | 283 | 157 | 111 | 122 |
| 81 | 7.5 | 7.5 | 116 | 109 | 225 | 201 | 92 | 89 | 79 |
| 82 | 9.0 | 8.0 | 138 | 132 | 270 | 278 | 146 | 103 | 106 |
| Mean | 8.5±0.5 | 8.0±0.5 | 130±6 | 128±7 | 260±15 | 251±24 | 123±24 | 97±8 | 94±6 |

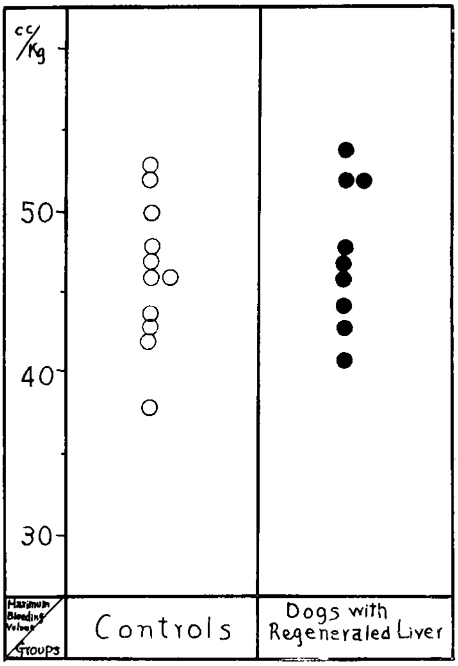
**Tab. 3** Hemorrhagic Shock by Wiggers' Method (Controls)

| Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding Volume cc/kg Body Wt. | Results | |
|---|---|---|---|---|---|---|
| | | | | | after 12 hrs. | after 24 hrs. |
| 1 | ♀ | 9.5 | 115 | 52 | Survived | 16.00 |
| 3 | ♂ | 8.0 | 130 | 46 | Survived | 14.00 |
| 5 | ♀ | 11.0 | 120 | 50 | 11.20 | — |
| 7 | ♂ | 9.0 | 130 | 46 | Survived | Survived |
| 9 | ♂ | 10.0 | 130 | 42 | Survived | 16.00 |
| 70 | ♂ | 8.0 | 125 | 44 | 7.50 | — |
| 73 | ♀ | 8.5 | 120 | 47 | Survived | 13.00 |
| 74 | ♀ | 8.0 | 110 | 38 | 9.40 | — |
| 77 | ♂ | 8.5 | 110 | 48 | Survived | Survived |
| 78 | ♂ | 8.5 | 130 | 53 | 8.30 | — |
| 79 | ♀ | 9.0 | 110 | 43 | 11.40 | — |
| Mean | | 8.5±0.5 | 120±10 | 46±3 | Survived/Total | |
| | | | | | 6/11 | 2/11 |

**Tab. 4** Hemorrhagic Shock by Wiggers' Method (Dogs with Regenerated Liver)

| Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding Volume cc/kg Body Wt. | Results | |
|---|---|---|---|---|---|---|
| | | | | | after 12 hrs. | after 24 hrs. |
| 2 | ♂ | 9.0 | 110 | 54 | Survived | 17.00 |
| 4 | ♀ | 9.5 | 120 | 47 | Survived | 14.00 |
| 6 | ♂ | 7.5 | 120 | 44 | 10.30 | — |
| 8 | ♀ | 9.0 | 110 | 46 | 11.40 | — |
| 81 | ♀ | 7.5 | 140 | 52 | Survived | Survived |
| 82 | ♂ | 8.0 | 120 | 48 | 8.40 | — |
| 84 | ♀ | 8.5 | 130 | 41 | Survived | 13.00 |
| 87 | ♀ | 7.5 | 130 | 52 | 9.20 | — |
| 88 | ♂ | 10.0 | 120 | 43 | Survived | Survived |
| Mean | | 8.5±0.5 | 120±5 | 47±4 | Survived/Total | |
| | | | | | 5/9 | 2/9 |

**Fig. 4** Maximum Bleeding Volume in Hemorrhagic Shock by Wiggers' Method




i. Group of blood returning at the time of 15 per cent spontaneous returning

Entire withdrawn blood was returned at the time of 15 per cent spontaneous retruning in 3 control and 3 experimental dogs. The obtained results are summarized in Tab. 5.

Maximum bleeding volume was from 41 to 50 cc/kg body weight, 45±3 cc/kg body weight on the average, in control group, while in experimental group it was from 42 to 49 cc/kg body weight, 46±3 cc/kg body weight on the average, showing no marked difference between these 2 groups.

Spontaneous returning time in control group was from 2 to 3 hours, 2 hours and 30 minutes ±20 minutes on the average, and in experimental group it was from 1 hour and 50 minutes to 2 hours and 50 minutes, 2 hours and 20 minutes ±20 minutes on the average, also revealing no significant difference between these 2 groups.

Twenty-four hour survival rate in control group was 3/3 (100 per cent) and it was also 3/3 (100 per cent) in experimental group. Thus, there was no significant difference in these 2 groups, all the animals in both groups surviving.

ii. Group of blood returning at the time of 30 per cent spontaneous returning

The results of blood returning at the time of 30 per cent spontaneous returning in 16 control and 14 experimental dogs are summarized in Tab. 6 and Tab. 7.

a. Maximum bleeding volume

As shown in Fig. 5, maximum bleeding volume in control group was from 34 to

**Tab. 5** Cases with Arterial Infusion at the Stage of 15% Spontaneous Blood Return

| | Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding Volume | | Time to spont. Blood Return | | Results |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time to hrs. mins. | cc/kg Body Wt. | Beginning | 15% | |
| Controls | 31 | ♀ | 12.0 | 130 | 1.50 | 50 | 3.00 | 3.10 | Survived |
| | 33 | ♀ | 9.5 | 130 | 2.00 | 44 | 2.40 | 1.00 | Survived |
| | 36 | ♂ | 7.5 | 110 | 1.20 | 41 | 2.00 | 2.50 | Survived |
| | Mean | | 10.0±1.5 | 120±10 | 140±20 | 45±3 | 2.30±20 | 3.30±30 | |
| Dogs with Regenerated Liver | 41 | ♀ | 9.0 | 130 | 1.40 | 49 | 2.30 | 3.40 | Survived |
| | 42 | ♂ | 8.5 | 120 | 1.10 | 42 | 1.50 | 2.40 | Survived |
| | 43 | ♂ | 10.0 | 110 | 1.50 | 47 | 2.50 | 3.20 | Survived |
| | Mean | | 9.0±0.5 | 120±10 | 1.30±20 | 46±3 | 2,20±20 | 3.10±20 | |

52 cc/kg body weight, 44±4 cc/kg body weight on the average, and in experimental group it was from 36 to 53 cc/kg body weight, 45±4 cc/kg body weight on the average, showing no marked difference in these 2 groups.

b. Time-span to maximum bleeding volume

As shown in Fig. 6, time-span to maximum bleeding volume in control group was from 50 minutes to 2 hours and 50 minutes, 1 hour and 40 minutes ± 20 minutes on the average, while in experimental group it was from 1 hour to 2 hours and 50 minutes, 1 hour and 50 minutes ± 30 minutes on the average. Although the results of the 2 groups spread considerably in a wide range, there was no significant difference between these 2 groups.

c. Time-span to spontaneous returning

As shown in Fig. 6, time-span to spontaneous returning in control group was from 1 hour and 40 minutes to 4 hours and 10 minutes, 2 hours and 40 minutes ± 30 minutes on the average, and in experimental group it was from 1 hour and 30 minutes to 3 hours and 50 minutes, 2 hours and 50 minutes ± 40 minutes on the average. Although the results of the 2 groups were scattered in a wide range, there could not be observed any significant difference in these 2 groups.

d. Time-span to 30 per cent spontaneous returning

As shown in Fig. 6, time-span to 30 per cent spontaneous returning in control group was from 3 hours to 6 hours and 40 minutes, 4 hours and 50 minutes ± 50 minutes on the average, and in experimental group it was from 3 hours and 30 minutes to 7

**Tab. 6** Cases with Arterial Infusion at the Stage of 30% Spontaneous Blood Return (Controls)

| Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding Volume: Time to hrs. mins. | Max. Bleeding Volume: cc/kg Body Wt. | Time to Spont. Blood Return: Beginning | Time to Spont. Blood Return: 30% | Results: after 12 hrs. | Results: after 24 hrs. |
|---|---|---|---|---|---|---|---|---|---|
| 11 | ♂ | 8.5 | 140 | 2.10 | 47 | 3.20 | 5.50 | Survived | 17.00 |
| 16 | ♀ | 8.5 | 125 | 1.40 | 43 | 2.50 | 4.40 | 11.40 | — |
| 17 | ♂ | 10.0 | 115 | 2.50 | 43 | 4.10 | 6.40 | Survived | 14.00 |
| 18 | ♂ | 8.5 | 135 | 1.20 | 45 | 2.40 | 5.20 | Survived | |
| 34 | ♂ | 10.0 | 120 | 1.30 | 39 | 2.10 | 3.40 | 9.20 | — |
| 35 | ♀ | 9.0 | 115 | 1.50 | 47 | 2.40 | 5.10 | Survived | 13.00 |
| 37 | ♂ | 8.5 | 120 | 1.40 | 50 | 3.00 | 1.10 | 10.00 | — |
| 38 | ♂ | 10.5 | 140 | 1.20 | 42 | 2.50 | 5.50 | Survived | Died |
| 52 | ♀ | 9.0 | 120 | .50 | 36 | 1.40 | 3.00 | 9.20 | — |
| 53 | ♂ | 8.0 | 140 | 1.20 | 34 | 1.50 | 3.30 | 8.40 | — |
| 55 | ♀ | 8.0 | 125 | 1.30 | 43 | 1.50 | 3.20 | 7.50 | — |
| 56 | ♂ | 8.5 | 115 | 1.40 | 43 | 2.20 | 5.00 | 10.30 | — |
| 71 | ♀ | 7.0 | 130 | 1.50 | 52 | 2.50 | 5.10 | 11.50 | — |
| 72 | ♂ | 9.0 | 125 | 2.20 | 44 | 3.50 | 6.20 | Survived | Died |
| 74 | ♀ | 7.5 | 115 | 2.20 | 46 | 3.10 | 6.00 | 9.40 | — |
| 76 | ♀ | 8.5 | 110 | 1.40 | 47 | 2.30 | 4.30 | Survived | 13.00 |
| Mean | | 8.5±1.0 | 125±10 | 1.40±20 | 44±4 | 2.40±30 | 4.50±50 | Survived/Total 7/16 | 0/16 |

**Tab. 7** Cases with Arterial Infusion at the Stage of 30% Spontaneous Blood Return (Dogs with Regenerated Liver)

| Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding Volume | | Time to Spont. Blood Return | | Results | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Time to hrs. mins. | cc/kg Body Wt. | Beginning | 30% | after 12 hrs. | after 24 hrs. |
| 23 | ♀ | 8.0 | 135 | 2.20 | 46 | 3.50 | 6.40 | Survived | Died |
| 24 | ♂ | 9.5 | 140 | 2.00 | 44 | 3.00 | 4.50 | 10.50 | — |
| 25 | ♂ | 9.0 | 125 | 2.20 | 49 | 3.30 | 6.00 | Survived | 14.00 |
| 26 | ♂ | 10.0 | 115 | 1.50 | 53 | 2.50 | 5.40 | 9.40 | — |
| 45 | ♀ | 8.5 | 130 | 2.20 | 43 | 3.40 | 7.10 | Survived | 17.00 |
| 46 | ♀ | 8.0 | 115 | 1.20 | 48 | 2.00 | 5.40 | 11.10 | — |
| 47 | ♂ | 7.5 | 110 | 2.50 | 46 | 3.00 | 6.30 | Survived | 15.00 |
| 62 | ♀ | 7.5 | 110 | 1.00 | 38 | 1.50 | 3.30 | 8.50 | — |
| 63 | ♀ | 11.0 | 125 | 1.40 | 40 | 2.30 | 5.00 | 11.20 | — |
| 66 | ♂ | 8.5 | 120 | 1.20 | 36 | 2.00 | 4.10 | Survived | 13.00 |
| 67 | ♀ | 7.5 | 120 | 1.10 | 43 | 1.30 | 3.40 | 8.30 | — |
| 83 | ♀ | 7.5 | 125 | 2.20 | 44 | 3.40 | 6.50 | Survived | Died |
| 85 | ♀ | 9.0 | 135 | 1.40 | 49 | 2.50 | 4.10 | 9.40 | — |
| 86 | ♂ | 8.0 | 120 | 2.10 | 51 | 2.20 | 5.50 | Survived | 13.00 |
| Mean | | 8.5±0.5 | 125±5 | 1.50±30 | 45±4 | 2.50±40 | 5.30±60 | Survived/Total | |
| | | | | | | | | 7/14 | 0/14 |

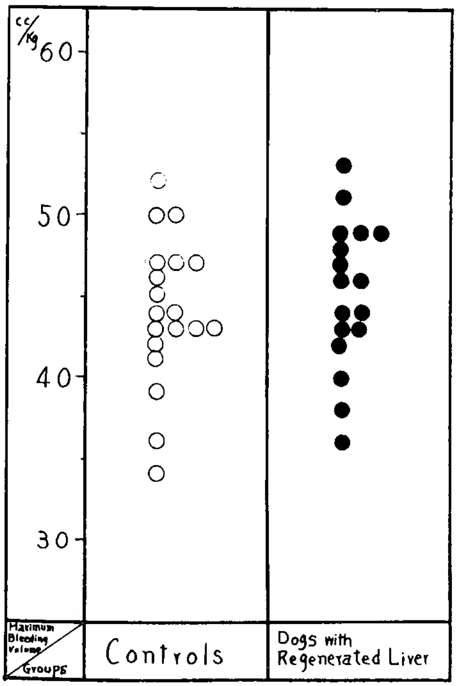



**Fig. 5** Maximum Bleeding Volume in Hemorrhagic Shock by Modified Method of Lamson

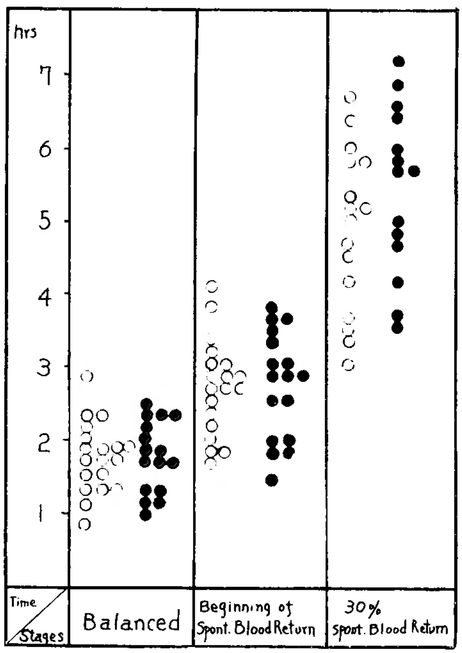



**Fig. 6** Time to Stages of Balanced, Beginning and 30% Spontaneous Blood Return –Controls –Dogs with Regenerated Liver

hours and 10 minutes, 5 hours and 30 minutes ± 60 minutes on the average, revealing a slight prolongation in this group. The results in both groups widely spreading, it was difficult to notice recognizable marked difference between these 2 groups.

e. Survival rate

Twelve hour survival rate in control group was 7/16 (44 per cent) and 24 hour survival rate 0/16 (0 per cent), and in experimental group the former was 7/14 (50 per cent) and the latter also 0/14 (0 per cent). All the animals died until 24 hours after surgery in both groups and there was no significant difference in these 2 groups.

f. Influence of sex on the results

Since the results of both control and experimental group were scattered in a wide range in the experiment following the modified method of LAMSON, some possibility of influence of sex on the results was presumed and analysis on this point was attempted.

Concerning maximum bleeding volume, as shown in Fig. 7, average value of male dogs in control group was 43±2 cc/kg body weight and that of female dogs in the same group was 45±2 cc/kg body weight, while in experimental group average value of male dogs was 46±4 cc/kg body weight and that of female dogs in the latter group was 44±3 cc/kg. Thus, even in analysis based on sexes, significant difference could not be found between these 2 groups.

As shown in Fig. 8, spontaneous returning time of male dogs in control group was 2 hours and 50 minutes ± 30 minutes, on the average, and that of female dogs in the

**Fig. 7** Relationship between Maximum Bleeding Volume and Sex in Hemorrhagic Shock by Modified Method of Lamson

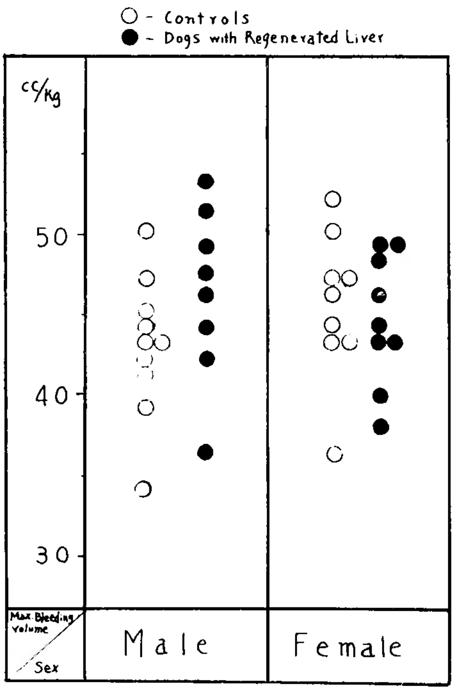
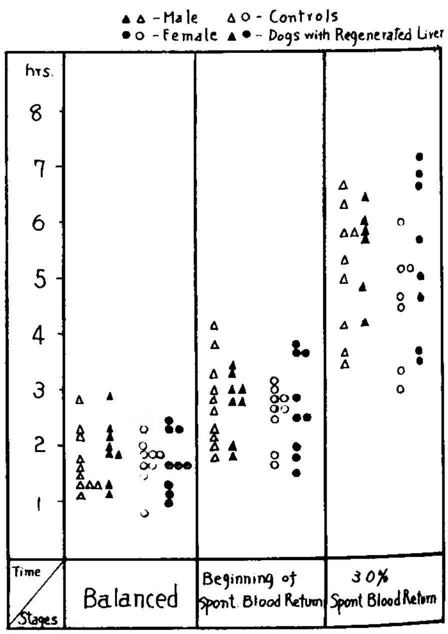



**Fig. 8** Relationship between Sex and Period of Time to Stages of Balanced, Beginning and 30% Spontaneous Blood Return



same group was 2 hours and 30 minutes ± 30 minutes, on the average, while that of male dogs in experimental group was 2 hours and 50 minutes ± 30 minutes, on the average, and that of female dogs of the latter group was 2 hours and 40 minutes ± 40 minutes, on the average, showing no obvious difference between both sexes and both groups.

g. Relation to temperature

During the course of experiments following the modified method of LAMSON, some correlation between the results and temperature was infered and it was considered that this interference of temperature might be a cause of so much scattered results of experiments. Therefore, from a presumption that some significant difference would be sought between control and experimental groups, when the results of experiment are analysed excluding the interference of temperature, experimental results were analysed on this presumption. Namely, experiments following modified method of LAMSON carried out during the period of 1 year from September 15, 1963 to September 14, 1964 were divided into 4 groups ; experiments done from September 15 to December 14, (Dog No. 1—9, 70—89) in autumn, experiments done from December 15 to March 14, (Dog No. 10—29) in winter, experiments done from March 15 to June 14, (Dog No. 30—49) in spring and experiments done from June 15 to September 14, (Dog No. 50—69) in summer.

**Tab. 8** Relalionship between Hemorrhagic Shock and Temperature (Controls)

| Seasons | Dogs | Mean Temperature °C | Time to Max. Bleeding Volume hrs. mins. | Max. Bleeding Volume cc/kg Body Wt. | Time to Spont. Blood Return hrs. mins. | Survival Ratio after 12 hrs. |
|---|---|---|---|---|---|---|
| 15. Dec. ~14. Mar. | 4 | 5.0 | 2.30±30 | 44±3 | 3.15±30 | 3/4 |
| 15. Mar. ~14. Jun. | 7 | 15.5 | 1.50±10 | 45±4 | 2.40±20 | 2/4* |
| 15. Jun. ~14. Sept. | 4 | 25.4 | 1.20±20 | 38±3 | 1.55±10 | 0/4 |
| 15. Sept. ~14. Dec. | 4 | 12.1 | 2.00±20 | 47±2 | 3.10±30 | 2/4 |
| Mean | 19 | 14.5 | 1.40±20 | 44±4 | 2.40±30 | 7/16 |

**Tab. 9** Relationship between Hemorrhagic Shock and Temperature (Dogs with Regenerated Liver)

| Seasons | Dogs | Mean Temperature °C | Time to Max. Bleeding Volume hrs. mins. | Max. Bleeding Volume cc/kg Body Wt. | Time to Spont. Blood Return hrs. mins. | Survival Ratio after 12 hrs. |
|---|---|---|---|---|---|---|
| 15. Dec. ~14. Mar. | 4 | 5.0 | 2.10±5 | 48±3 | 3.20±20 | 2/4 |
| 15.Mar. ~14. Jun. | 6 | 15.5 | 1.50±30 | 46±2 | 2.50±30 | 2/3* |
| 15. Jun. ~14. Sept. | 4 | 25.4 | 1.20±10 | 39±2 | 2.00±20 | 1/4 |
| 15. Sept. ~14. Dec. | 3 | 12.1 | 2.00±20 | 48±3 | 3.20±20 | 2/3 |
| Mean | 17 | 14.5 | 1.50±30 | 45±4 | 2.50±30 | 7/14 |

* Other 3 dogs out of 7 were subjected to cases with arterial infusion at the stage of 15% spontaneous blood return in hemorrhagic shock by modified method of Lamson.

Based on this classification, maximum bleeding volume, time-span to maximum bleeding, time-span to spontaneous returning, time-span to 30 per cent spontaneous returning and 12 hour survival rate were studied, as represented in Tab. 8 and Tab. 9. Average temperature at noon was 12.1°C in autumn, 5.0°C in winter, 15.5°C in spring and 25.4°C in summer, year round average temperature being 14.5°C.

Concerning maximum bleeding volume, as shown in Fig. 9, the values were lower in summer to be 38±3 cc/kg body weight in control group on the average and 39±2 cc/kg body weight in experimental group on the average, being lower than year round average value of 44±4 cc/kg body weight in control group and 45±4 cc/kg body weight in experimental group. The largest value in this season was close to the smallest value in other three seasons. However, significant difference could not be observed between these 2 groups, even when the influence of seasons was taken into consideration.

Spontaneous returning time and time-span to 30 per cent spontaneous returning were also obviously shorter in summer in both groups compared with those in other three seasons.

Twelve hour survival rate in control group was 0/4 (0 per cent) in summer, whereas in other three seasons it was 7/12 (58 per cent), and in experimental group it was 1/4 (25 per cent) in summer, whereas it was 6/10 (60 per cent) in other three seasons, both showing obviously lower value in summer. However, there was no significant difference between control and experimental groups, even though the influence of seasons was taken into consideration.

As obvious from these findings, the results were worse in summer. Hereupon, the

**Fig. 9** Relationship between Temperature and Maximum Bleeding Volume

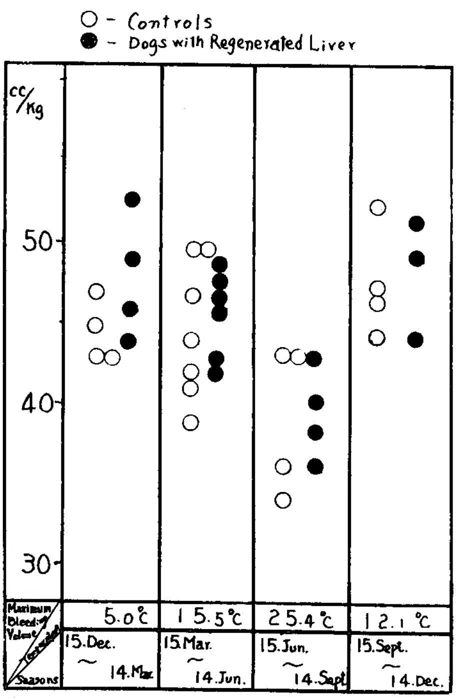
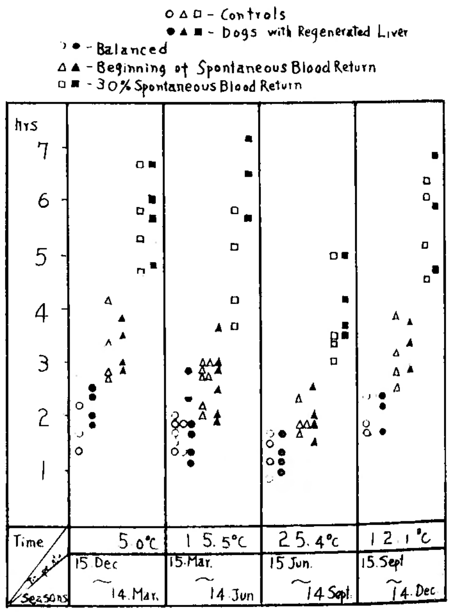



**Fig. 10** Relationship between Temperature and Time to Stages of Balanced, Beginning and 30% Spontaneous Blood Return



results obtained during summer season was excluded and those of blood returning at the time of 15 and 30 per cent spontaneous returning in control and experimental groups were compared with each other. Maximum bleeding volume in control group was 45±4 cc/kg body weight on the average and 47±3 cc/kg body weight in experimetal group, revealing no marked difference. Time-span to maximum bleeding volume was 1 hour and 50 minutes ± 20 minutes on the average in control group, while it was 2 hours ± 20 minutes on the average in experinental group, and no significant difference could be observed. Spontaneous returning time was 2 hours and 50 minutes ± 20 minutes and 3 hours ± 30 minutes in experimental group, also revealing no marked difference. Time-span to 30 per cent spontaneous returning was 5 hours and 20 minutes ± 40 minutes in control group and 6 hours ± 40 minutes in experimental group, showing no significant difference between 2 groups.

Twelve hour survival rate was 7/12 (58 per cent) in control group and 6/10 (60 per cent) in experimental group, similarly showing no significant difference.

From these findings, it is assumed that there existed no significant difference between control group and experimental group, even when the influence of the seasen was taken into consideration.

4. Changes in Portal Pressure

Hemorrhagic shock was produced following the modified method of LAMSON in 5 control dogs and 5 experimental dogs. Blood was returned at the time of 30 per cent spontaneous returning, and changes in portal pressure were simultaneously studied.

As represented in Tab. 10, Tab. 11 and Fig. 11, portal pressure before withdrawal of blood was from 111 $mmH_2O$ to 138 $mmH_2O$, 125±9 $mmH_2O$ on the average, in control group, while it was from 135 $mmH_2O$ to 154 $mmH_2O$, 146 $mmH_2O$ on the average, in experimental group, obviously showing higher level in the latter. As the

**Tab. 10** Changes of Portal Pressure in Hemorrhagic Shock by Modified Method of Lamson

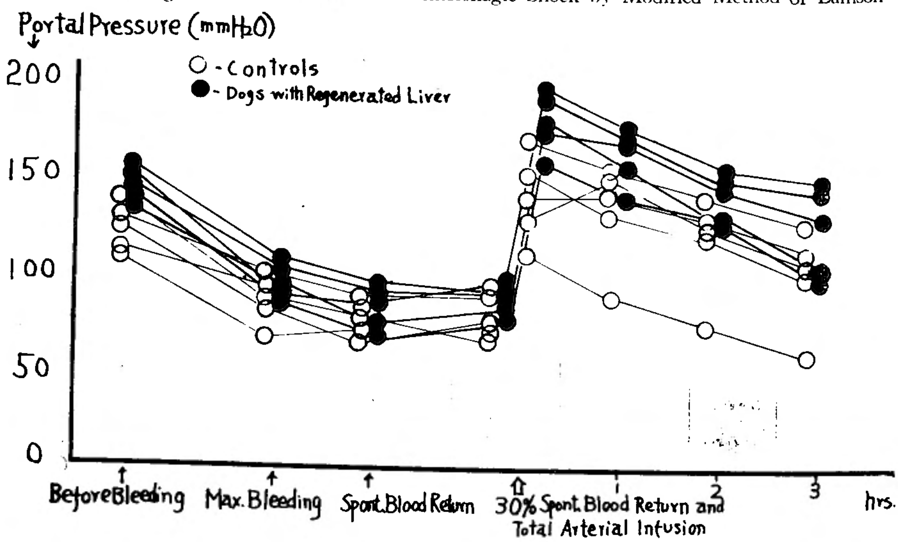
| | Dog No. | Sex | Body Wt. kg | Portal Press. before Bleeding $mmH_2O$ | Changes at the Stage of | | | After Total Arterial Infusion hrs. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Max. Bleeding Volume | Spont. Blood Return Biginning | Spont. Blood Return 30% | Diveetly after | 1 | 2 | 3 |
| Controls | 51 | ♀ | 8.5 | 131 | 100 | 87 | 86 | 150 | 134 | 120 | 100 |
| | 54 | ♀ | 8.5 | 124 | 82 | 66 | 76 | 138 | 141 | 129 | 110 |
| | 55 | ♂ | 9.0 | 138 | 94 | 84 | 94 | 169 | 156 | 139 | 125 |
| | 57 | ♂ | 10.0 | 120 | 91 | 75 | 68 | 109 | 92 | 75 | 60 |
| | 58 | ♀ | 9.0 | 111 | 73 | 69 | 73 | 129 | 150 | 121 | 106 |
| | Mean | | | 125±9 | 88±8 | 75±6 | 79±8 | 139±16 | 135±16 | 117±17 | 100±16 |
| Dogs with Regenerated Liver | 61 | ♀ | 9.0 | 154 | 106 | 94 | 96 | 188 | 168 | 148 | 141 |
| | 64 | ♀ | 7.5 | 150 | 102 | 90 | 90 | 170 | 163 | 142 | 129 |
| | 65 | ♀ | 8.5 | 152 | 97 | 86 | 100 | 194 | 175 | 156 | 147 |
| | 68 | ♂ | 9.0 | 140 | 84 | 71 | 78 | 156 | 137 | 129 | 104 |
| | 69 | ♂ | 9.0 | 135 | 91 | 78 | 87 | 172 | 156 | 126 | 96 |
| | Mean | | | 146±7 | 96±7 | 84±7 | 90±6 | 176±12 | 100±11 | 140±10 | 123±20 |

withdrawal of blood was started, portal pressure began to decrease in parallel with rapid fall in arterial pressure in both groups, although the degree of decrease was smaller in portal pressure. Changes in portal pressure were ever resembling to each other in control group and experimental group, which reached the lowest level at spontaneous returning time, corresponding to 60 per cent and 58 per cent in control group and experimental group, respectively. Portal pressure turned to increase in most cases at the time of 30 per cent spontaneous retruning. By the blood returning at 30 per cent spontaneous returning, arterial pressure mostly restored to 90 per cent of the level before withdrawal of

**Tab. 11** Changes of Arterial Pressure in Cases with Measurement of Portal Pressure in Hemorrhagic Shock by Modified Method of Lamson

| | Dog No. | Sex | Body Wt. kg | Max. Bleeding Volume: Time to hrs. mins. | Max. Bleeding Volume: cc/kg Body Wt. | Time to Spont. Blood Reture: Beginning | Time to Spont. Blood Reture: 30% | Arterial pressure before Bleeding $mmH_2O$ | After Total Arterial Reinfusion hrs.: Dierctly soon | 1 | 2 | 3 | Surrival Time |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Controls | 51 | ♀ | 8.5 | .50 | 39 | 1.40 | 2.40 | 120 | 105 | 80 | 65 | 55 | 7.00 |
| | 54 | ♀ | 8.5 | 1.20 | 41 | 2.00 | 3.20 | 110 | 120 | 105 | 90 | 75 | 9.20 |
| | 55 | ♂ | 9.0 | 1.10 | 46 | 3.00 | 4.00 | 140 | 125 | 100 | 95 | 60 | 8.40 |
| | 57 | ♂ | 10.0 | 1.00 | 36 | 2.10 | 2.50 | 115 | 100 | 70 | 55 | 50 | 6.50 |
| | 58 | ♀ | 9.0 | 1.30 | 39 | 2.10 | 3.30 | 125 | 110 | 85 | 70 | 65 | 8.00 |
| | Mean | | | 1.20±20 | 40±3 | 2.20±30 | 3.20±20 | 120 | 110±10 | 90±10 | 75±15 | 60±10 | 8.00±50 |
| Dogs with Regenerated Livers | 61 | ♀ | 9.0 | 1.40 | 41 | 1.50 | 3.40 | 120 | 135 | 120 | 90 | 75 | 8.50 |
| | 64 | ♀ | 7.5 | .50 | 38 | 2.20 | 4.00 | 110 | 95 | 90 | 75 | 70 | 9.00 |
| | 65 | ♀ | 8.5 | 1.30 | 41 | 2.00 | 5.10 | 110 | 110 | 110 | 100 | 80 | 10.00 |
| | 68 | ♂ | 9.0 | 1.50 | 37 | 2.40 | 1.40 | 120 | 100 | 80 | 60 | 50 | 8.40 |
| | 69 | ♂ | 9.0 | 1.00 | 46 | 2.20 | 3.00 | 140 | 125 | 100 | 85 | 60 | 7.20 |
| | Mean | | | 1.20±20 | 40±3 | 2.10±20 | 1.10±40 | 120 | 115±15 | 100±10 | 80±10 | 70±10 | 8.50±40 |

**Fig. 11** Changes of Portal Pressure in Hemorrhagic Shock by Modified Method of Lamson

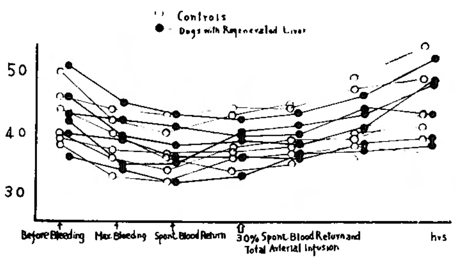


blood, whereas portal pressure showed marked increase in both groups, exceeding the level before withdrawal of blood. Rate of increase in portal pressure after returning of blood in experimental group was slightly higher to 120 per cent compared with the average value of 110 per cent in control group. Portal pressure behaved in a similar tendency in both groups in parallel with a decrease in arterial pressure thereafter, although the former was maintained in relatively high level.

5. Changes in Hematocrit Ratio

Hematocrit ratio was determined in 6 control and 6 experimental dogs of blood returning at 30 per cent spontaneous returning in modified method of LAMSON. As shown in Tab. 12 and Fig. 12, hematocrit ratio before withdrawal of blood in control group was from 38 to 50 per cent, $45\pm4$ per cent on the average, and it was from 36 to 51 per cent, $43\pm4$ per cent on the average, in experimental group. The value decreased gradually in both groups in parallel with blood withdrawal, which remained in lower level at balanced stage and stage of spontaneous returning. Hematocrit ratio began to increase again towards the time of 30 per cent spontaneous returning. It increased on after returning of blood, in most cases showing a tendency of blood condensation exceeding the level before withdrawal of blood, 4 hours and 30 minutes after retunning of blood.

**Fig. 12** Changes of HematocritRatio in Hemorrhagic Shock by Modified Method of Lamson




6. Histological Findings

As shown in Tab. 13, hemorrhagic shock was produced by modified method of LAMSON without returning of blood in 1 control and 1 experimental dogs. Obtained histological find-

**Tab. 12** Changes of Hematocrit Ratio With the Lapse of Time in Hemorrhagic Shock by Modified Method of Lamson

| | Dog No. | Sex | Body Wt. kg | Before Bleeding | Changes at the Stage of Max. Bleeding Volume | Spont. Blood Return Beginning | Spont. Blood Return 30% | After Total Arterial Infusion 1.5 hrs | 3 hrs. | 4.5 hrs |
|---|---|---|---|---|---|---|---|---|---|---|
| Controls | 16 | ♀ | 9.5 | 40 | 36 | 34 | 37 | 39 | 39 | 43 |
| | 34 | ♂ | 10.0 | 39 | 37 | 36 | 37 | 38 | 40 | 41 |
| | 37 | ♂ | 8.5 | 38 | 33 | 32 | 36 | 37 | 38 | 37 |
| | 53 | ♂ | 8.0 | 50 | 42 | 40 | 44 | 45 | 49 | 54 |
| | 72 | ♂ | 9.0 | 46 | 44 | 43 | 43 | 45 | 47 | 49 |
| | 74 | ♀ | 8.5 | 44 | 40 | 36 | 34 | 35 | 36 | 39 |
| Dogs with Regenerated Liver | 23 | ♀ | 80 | 36 | 34 | 32 | 33 | 36 | 37 | 38 |
| | 45 | ♂ | 90 | 46 | 39 | 38 | 39 | 38 | 41 | 48 |
| | 46 | ♂ | 75 | 43 | 42 | 41 | 40 | 40 | 43 | 43 |
| | 63 | ♀ | 110 | 40 | 39 | 36 | 36 | 36 | 38 | 39 |
| | 85 | ♀ | 80 | 51 | 45 | 43 | 43 | 43 | 46 | 52 |
| | 86 | ♂ | 80 | 42 | 35 | 35 | 41 | 41 | 43 | 48 |

**Tab. 13** Cases with Histological Observation of Liver in Hemorrhagic Shock by Modified Method of Lamson

| | Dog No. | Sex | Body Wt. kg | Arterial Pressure mmHg | Max. Bleeding | | Time to Spontaneous Blood Return from the Time of Bleeding hrs. mins. | | | | | Surrival Time |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time to hrs. mins. | cc/kg Body Wt. | Beginn-ing | 30% | 50% | 70% | 100% | |
| Control | 32 | ♀ | 12.0 | 130 | 2.00 | 43 | 2.30 | 4.00 | 5.40 | 6.50 | 8.20 | 8.40 |
| Dog withRegener-ated Liver | 44 | ♂ | 9.0 | 125 | 1.50 | 46 | 2.50 | 4.40 | 6.40 | 7.40 | 9.00 | 9.20 |

ings are summarized as described in the below.

i. Before withdrawal of blood (Fig. 13, 14).

Slight cell infiltration in Glisson's sheath and irregularity of acinal structure could be observed here and there more frequently in regenerated liver than in control liver. No characteristic abnormality could be otherwise observed.

ii. At the time of spontaneous returning (Fig. 15, 16).

Congestion around the central veins and central sinusoids could be observed in both groups with accompanying hemosiderin granules in Kupffer cells and vacuole degeneration in some central liver cells. In regenerated liver, considerable infiltration of neutrophiles was observed.

iii. At the time of 30 per cent spontaneous returning (Fig. 17, 18).

The changes differed little essentially from those at the time of spontaneous returning, although they were slightly accentuated.

iv. At the time of 70 per cent spontaneous returning (Fig. 19, 20).

In both groups, atrophy of liver cells in the central area of the hepatic lobules was marked, and in some places destruction of small number of liver cells and neutrophile infiltration were observed. In the peripheral area of the hepatic lobules, hemorrhage was observed within Glisson's sheath frequently, with neutrophile infiltration and liver cell destruction around.

In general, regenerated liver sometimes showed considerably serious congestion and infiltration of neutrophiles and small round cells when compared with control liver. However, degeneration and atrophy of liver cells were a little more slight in regenerated liver than in control liver.

## IV. DISCUSSION

Concerning pathophysiology of the liver in hemorrhagic shock, numerous studies have been reported and the important role of the liver in such condition has been pointed out. In hemorrhagic shock, intrahepatic blood flow decreases remarkably[22], and the liver, which owes 80 per cent of its blood flow to the portal vein, encounters readily serious anoxia, partly due to remarkable decrease in oxygen content in portal blood[4]. Glycogen is released from the liver in early stage[41], and with a progressive decrease in oxygen consumption in the liver, glycogen content in the liver prominently decreases accompanied by marked decrease in high-energy phosphate of the liver[30][40], disturbance of enzymes and co-enzymes [11][48], decrease in production of albumin[10] prothrombin[17] and fibrinogen[18][21], release of kalium[41] and increase in amino-acid content in blood[33]. It is widely known that this series of these phenomenon progresses closely in parallel with the degree of liver failure due to anoxia. SHORR[42] pointed out that VDM is produced in the anoxic liver, and increase in this substance is a cause of irreversible shock. FINE[13] emphasized, in this respect, proliferation of intrahepatic anaerobic bacteria caused by liver anoxia and toxin produced by this bacteria. COHN[9] increased remarkably survival rate of shock by increasing arterial inflow to the liver, in his experiment using liver perfusion. From these observations, it is assumed that the liver is not only so much susceptible to anoxia in hemorrhagic shock, but playing decisive role in the development of irreversible shock.

Now-a-days, liver resection is considered to be a principal therapeutic maneuver for surgical diseases of the liver, and it is widely carried out. Accordingly, the patients having regenerated liver are largely increasing in number, and it is necessarily considered that occasion, in which such patients undergo surgical intervention for the second time, is ever increasing. It is not only of pathological but of clinical importance to investigate whether or not the regenerated liver, which is not less than normal liver in its weight and size, shows characteristic response to the large alterations caused by surgery with or without some resistance in such occasions, when it is considered that the liver plays an important role, as mentioned in the above, against aggressions. From this point of view, experimental regenerative liver was produced in dogs and its response to hemorrhagic shock, which is assumed to influence the liver so largely, was investigaled.

According to the reports of FISCHBACK[14], MANN[7], Grindley et BOLLMAN and others, weight of the residual liver parenchyma restores to preoperative weight 4 to 6 weeks after liver resection of 70 per cent of the entire liver weight. Fisher[15] also observed the similar results of hepatic regeneration 1 month after hepatic resection of 43 per cent of the entire liver weight. In recent years, significance of portal blood[16], hepatic blood flow[15] and humoral factor[3] has been gradually clarified. Considering these points, liver resection was carried out in the present experiment to the extent of 50 per cent of the entire liver weight, which scarcely causes stricture of the portal vein and is carried out by simple procedures with expectance of getting sufficient amount of liver regeneration. Experiment of hemorrhagic shock was performed 2 month after hepatic resection, at which period influence of hepatic resection itself can be made negligible as possible. At this period, the residual liver parenchyma showed 94 per cent of regeneration rate and decrease in red blood cell count observed shortly after liver resection already restored to preoperative level. Accordingly, it was assumed that volume of hepatic resection and interval of time between the resection and production of hemorrhagic shock was approximately adequate for the purpose of the present experiment.

Many methods have been reported on the production of hemorrhagic shock. Among these, WIGGERS reported that normovolemic shock state can be produced by inducing hypostatic condition in two phases and by returning the entire withdrawn blood after maintaining blood pressure in a low level for certain period of time. By this method, however, it is not always successful to produce irreversible shock and WIGGERS reported himself that the rate was 82 per cent. In the present experiment also, 24 hour survival rate in control group showed approximately similar result of 2/11 (19 per cent). On the other hand, LAMSON devised to produce hemorrhagic shock using a bottle for blood withdrawal, in which blood pressure can be held in any level of hypotension. Although duration of time of hypotensive state differs considerably depending upon individuality by this method of hemorrhagic shock, withdrawn blood in the bottle begins to return to the organism spontaneously as the compensatory capacity of animals is exhausted out after certain interval of time. Using this method, FINE observed that irreversible shock can be produced if all the remaining blood within the bottle is returned to the body at the moment when the volume of spontaneous return reaches 30 to 40 per cent of the maximum bleeding volume. When this method was employed in the present experiment, all the control animals survived when the blood in the bottle was returned at 15 per cent spontaneous returning, and all the animals died when the blood in the bottle was returned at 30 per cent spontaneous returning. Hence, it was assumed that this method was the most suited to the aim of the present experiment, since by this method reversible and irreversible shock can be produced *ad libitum* and observation can be done preciously during the experiment.

It was pointed out by ALLEN[1], BERGMANN[5] and others that shock is closely related to temperature and weather. BLALOCK[6] observed prolongation of shock state in chilly condition, and REMINGTON[39] reported that for the production of the identical degree of shock state, bleeding volume should be increased in winter. In the present experiment, results obtained during summer showed less maximum bleeding volume, shortening of spontaneous returning time and decrease in survival rate in control and experimental groups compared with those obtained in other three seasons, obviously revealing decrease in shock resistance. It is assumed that this should be carefully taken into account at the comparison of the experimental results. In this respect, experiment employing WIGGERS' method was carried out during the period from September to December, in which temperature and weather is considered to have little influence on the experimental results, and analysis of the experimental results by modified method of LAMSON was done with this consideration.

In the results of experiment of hemorrhagic shock by WIGGERS' method, maximum bleeding volume in control dogs was $46 \pm 3$ cc/kg body weight on the average, and that of experimental dogs was in the similar level to be $47 \pm 4$ cc/kg body weight on the average. Twelve hour survival rate in control group was 6/11 (54 per cent), and it was 5/9 (56 per cent) in experimental group. Twenty-four hour survival rates were 2/11 (18 per cent) and 2/9 (22 per cent), respectively in control group and experimental group, also showing no marked difference from each other. Principal aim of Wiggers' method consists in producing hemorrhagic shock of identical condition by maintaining certain hypotensive state for certain length of time taking arterial pressure as an indicator. It is considered that there exist some occasions in which the state of shock still remains in a reversible phase under such conditions without being driven to irreversible phase, partly owing to individual difference in compensatory capacity. In fact, in the present experiment, approximately 20 per cent of the animals still survived 24 hours after production of shock state in control group, despite, on the other hand, animals of as many as 50 per cent died 12 hours after production of shock state. Accordingly, as was pointed out by WIGGERS' himself, influences of individuality cannot be neglected. Although it was difficult to find difference to be mentioned in the experimental results between control group and experimental group, as described in the above, conclusion as to the superiority or inferiority of experimental animals cannot be readily drawn.

On the other hand, in the results of experiment by modified method of Lamson, significant difference could not be observed between control group and experimental group in maximum bleeding volume, spontaneous returning time and time-span to 15 per cent spontaneous return, when the blood within the bottle was returned at the time of 15 per cent spontaneous return. Significant difference could not be observed also in 24 hour survival rate and the animals of both groups invariably survived. This finding is interpreted that the animals preserve the capacity to restore around the time of 15 per cent spontaneous return, even if compensatory mechanism of circulatory system is disturbed by continuation of hypotensive state caused by withdrawal of blood. It is assumed that, in this respect, both control and experimental animals have similar response. When the blood within the bottle was returned at the time of 30 per cent spontaneous return, maximum bleeding volume in control group was $44\pm4$ cc/kg body weight, and it was $45\pm4$ cc/kg body weight in experimental group, respectively on the average. Time-span to maximum bleeding volume was 1 hour and 40 minutes $\pm$ 20 minutes on the average in control group, and it was 1 hour and 50 minutes $\pm$ 30 minutes on the average in experimental group. Spontaneous returning time in control group was 2 hours and 40 minutes on the average, and it was 2 hours and 50 minutes $\pm$ 40 minutes on the average in experimental group. Time-span to 30 per cent spontaneous return was 4 hours and 50 minutes $\pm$ 50 minutes on the average in control group, and it was 5 hours and 30 minutes $\pm$ 60 minutes on the average in experimental group. Although these results are scattered in considerably wide range, they show similar tendency to each other revealing no marked difference between control and experimental groups, even when the results obtained during summer is excluded considering the influence of seasons, as mentioned in the above. Twelve hour survival rate in control group was 7/16 (45 per cent), and 7/14 (50 per cent) in experimental group. Twenty-four hour survival rate was 0 per cent in both groups. Namely, animals in both groups showed definitely similar results. Towards the time of 30 per cent spontaneous return, hematocrit ratio and portal pressure began to show obvious tendency of increase. FRIEDMAN and FINE[20] explained this finding to be due to increase in intrahepatic vascular resistance from the findings of hepatic angiography. Moreover, from the fact that from this stage hepatic $Qo_2$ rapidly decreases, it is assumed that hemorrhagic shock becomes irreversible in this stage[45]. In this respect also, the response was similar in control group and experimental group to each other.

Uncountable studies have been carried out on regeneration of residual liver parenchyma after extensive hepatic resection, and it is considered in general that the liver, which has accomplished regeneration, has nothing different from normal liver in histological appearance, cellular constitution and its function[27]. However, it is considered that reconstruction of intrahepatic vascular system is markedly retarded, despite early recovery in liver weight and its function[43]. This fact is understood from the results of the present experiment that portal pressure in control group was $125\pm9$ $mmH_2O$ on the average before the withdrawal of blood, whereas it was obviously in a higher level of 146±7 $mmH_2O$ in experimental group, on the average, when the blood within the bottle was returned at the time of 30 per cent spontaneous return. Recovery of portal pressure after the blood was returned at the time of 30 per cent spontaneous return was slightly higher to be 120 per cent in experimental group compared with that of 110 per cent in control group, being suggestive of larger vascular resistance of the intrahepatic portal system in experimental animals than in normal ones.

As has been discussed, an organism having regenerated liver did not show any recognizable difference in the result of hemorrhagic shock by the modified method of LAMSON and WIGGERS' method when compared with normal animals, despite its disadvantageous condition in hepatic circulation as presumed from the findings of portal pressure in the present experiment. Accordingly, it is at least assumed that the dogs with regenerated liver is in no way inferior to normal ones in the response to hemorrhagic shock, though it is a little excessive to say that the dogs with regenerated liver is more resistant to shock state of this kind than normal ones.

## V. SUMMARY

In order to study the attitude of organism having regenerated liver following hepatic resection against hemorrhagic shock, hemorrhagic shock was produced by the modified method of LAMSON and method of WIGGERS' in dogs having 2 month aged regenerated liver after 50 per cent hepatic resection. By the comparison of the results in these animals with those of normal ones, the following results were obtained.

1) In maximum bleeding volume in hemorrhagic shock by WIGGERS' method, significant difference could not be observed between control and experimental animals. Twelve and twenty-four hour survival rates were 6/11 (54 per cent) and 2/11 (18 per cent) in control animals, while they were 5/9 (56 per cent) and 2/9 (22 per cent) respectively in experimental animals, revealing no significant difference between these two groups.

2) In the experiment of hemorrhagic shock by modified method of Lamson, all the animals of both groups survived more than 24 hours, when the blood was returned at the time of 15 per cent spontaneous return, and when the blood was returned at the time of 30 per cent spontaneous return, all the animals in both groups died within 24 hours after withdrawal of blood.

3) There was no significant difference between control group and experimental group in maximum bleeding volume, time-span to maximum bleeding volume, spontaneous returning time, time-span to 15 and 30 per cent spontaneous return and 12 and 24 hour survival rates, regardless of the time of return of the blood within the bottle either at the time of 15 per cent or 30 per cent spontaneous return in the experiment by modified method of Lamson. Namely, significant difference could not be found out in the attitude of animals between these two groups in reversible and irreversible phase of hemorrhagic shock.

4) Portal pressure in experimental group was higher before withdrawal of blood and recovery rate of portal pressure after returning of the blood within the bottle was a

litter higher than in control group, suggesting a little larger vascular resistance in the intrahepatic portal system.

5) Changes in hematocrit ratio in experimental group showed similar tendency as in control group, revealing no significant difference from each other.

6) From these findings, it is assumed that the dogs with regenerated liver show the similar response to hemorrhagic shock as control dogs without revealing inferiority in this respect.

Accomplishing the present paper, the author is deeply indebted to Prof. Dr. Ichio Honjo for his encouragement and valuable advices throughout the course of the present experiment.

## REFERENCES


1) Allen, F. A. : Surgical considerations of temperature in ligated limbs. Am. J. Surg. **45** : 459, 1939.
2) Allermann, K. : Some local factor in the restoration of the rats liver after partial hepatectomy. Arch. Path. **53** : 197, 1925.
3) Alson, W. C. : Humoral and local factor in liver regeneration. Cancer Res. **23** : 901, 1963.
4) Ballinger, W. F. and Vollenweider, H. : The effect of hemorrhage upon hepatic blood flow and splanchnic oxygen consumption in dogs. Surg. **48** : 758, 1960.
5) Bergman, H. C. and Prinzmetal, M. : Influence of environmental temperature on shock. Arch. Surg. **50** : 201, 1945.
6) Blalock, A. and Mason, M. F. : A comparison of the effects of heat and those of cold in the prevention and treatment of shock. Arch. Surg. **42** : 1054, 1941.
7) Bollman, J. L. and Mann, F. C. : The physiology of the impaired liver. Erg. Physiol. **38** : 445, 1936.
8) Boyce, F. F. : The so-called liver death in surgery. Surg. Gyne. and Obst. **61** : 122, 1935.
9) Cohn, R. and Parsons, H. : Relationship of portal hypertension and irreversibility of shock. Am. J. Physiol. **160** : 437, 1950.
10) Ebert, R. V., Stead, E. A. Jr., Warren, J. V. and Watts, W. E. : Plasma protein replacement after hemorrhage in dogs with and without shock. Am. J. Physiol. **136** : 299, 1942.
11) Engel, F. L. : Metabolic aspects of shock. problem. J. Mt. Sinai Hosp. **12** : 152, 1945.
12) Fine, J. Seligman, A. M. and Frank, H. A. : On the specific role of the liver in hemorrhagic shock. Ann. Surg. **126** : 1002, 1947.
13) Fine, J., Seligman, A. M. and Frank, H. A. : Role of the liver in shock. Ann. Surg. **122** : 652, 1945.
14) Fishback, F. C. : A morphologic study of regeneration of the liver after partial removal. Arch. Path. **7** : 955, 1927.
15) Fisher, B., Russ, C., Updegraff, H. and Ficher, E. R. : Effect of increased hepatic blood flow upon liver regeneration. Arch. Surg. **69** : 263, 1954.
16) Fisher, B., Lee, S. H., Fisher, E. R. and Saffer, E. : Liver regeneration following portacaval shunt. Surgery. **52** : 88, 1962.
17) Frank, E. D., Frank, H. A. and Fine, J. : Traumatic shock. XVIII. : Plasma prothrombin activity in hemorrhagic shock in dog. Am. J. Physiol. **167** : 499, 1951.
18) Frank, E. D., Frank, H. A. and Fine, J. : Traumatic shock. XVII. Plasma fibrinogen in hemorrhagic shock in dog. Am. J. Physiol. **162** : 619, 1950.
19) Frank, H. A. : Presentday concepts of shock. New Engl. J. Med. **249** : 445, 1953.
20) Friedman, F., Frank, H. A. and Fine, J. : Portal circulation in experimental hemorrhagic shock. Ann. Surg. **134** : 70, 1951.
21) Hardaway, R. M., Neimes, R. E., Burns, J. W., Mock, H. P. and Trenchack, P. T. : Role of the canine spleen in irreversible hemorrhagic shock. Ann. Surg. **156** : 197, 1962.
22) Hamrick, L. W. The effect of hemorrhage on hepatic blood flow and splanchnic oxygen consumption of dog. Circulation Res. **3** : 65, 1955.
23) Henschen, C. : Die Bedeutung der Leber in der Chirurgie. Arch. klin. Chir. **173** : 488, 1932.
24) Higgins, G. M. and Anderson, R. M. : Experimental pathology of the liver. Arch. Path. **12** : 186, 1931.
*25) Honjo, I. : On (sub-) total right hepatic lobectomy. Syuzyutsu **4** : 345, 1950.

26) Hyde, C. G. : The liver and its relaion to chronic abdominal infection. Ann. Surg. **79** : 55, 1924.
27) Islami, A. H., Pack, G. T., Schwartz, M. K. and Smith, E. R. : Regenerative hyperplasia of the liver following major hepatectomy. Ann. Surg. **150** : 85, 1959.
28) Keen, W. N. : Report of case of resection of the liver for removal of a meoplasm witha table of 76 cases of the liver for hepatic tumors. Ann. Surg. **30** : 267, 1887.
29) Lamson, P. D. and De Turk, W. E. : Studies on shock induced by hemorrhage. J. Pharmocol. and Exper. Therap. **83** : 250, 1945.
30) Le Page, G. A. : Effects of hemorrhage on tissue metabolites. Am. J. Physiol. **147** : 446, 1946.
31) Mann, F. C., Fishback, F. C., Gray, J. G. and Green, G. F. : Experimental pathology of the liver. Arch. Path. **72** : 787, 1936.
32) Martens, E. : Röntgenologische Studieren zur Arteriollen Gefässversorgung in der Leber. Arch. klin. Chir. **114** : 1001, 1920.
33) McShan, W. M., Potter, V. R., Goldman, A., Shipley, E. G. and Mever, R. K. : Biological energy transformations during shock as shown by blood chemistry. Am. J. Physiol. **145** : 93, 1945.
*34) Okumura, S. : Oxygraphic and histolgic studies on the liver function after massive hepatecomy. J. J. S. S. **58** : 1325, 1957.
35) Pack, G. T. and Baker, H. W. : Total right hepatic lobetomyc. Ann. Surg. **138** : 259, 1953.
36) Pack, G. T., Islami, A. H., Hubbard, J. C. and Brasfield, R. D. : Regeneraion of human liver after major hepatectomy. **52** : 617, 1962.
37) Pareira, M. D., Serkes, K. D. and Lang, S. : Tolerance of recently hemorrhaged rats to secondary trauma. Am. J. Physiol. **197** : 786, 1959.
38) Ponfick, E. : Experimentale Beigrage zur Pathologie der Leber. Virchow Arch. **118** : 209, 1889.
39) Remington, J. W., Hamilton, W. F., Caddell, H. M., Boyd, G. H., Wheeler, N. C. and Pickening, R. W. : Vasoconstriction as a precipitating factor in traumatic shock in the dog. Am. J. Physiol. **161** : 125, 1950.
40) Rosenbaum, D. K., Frank, E. D., Rutenburg, A. M. and Frank, H. A. : High-energy phosphate content of liver tissue in experimental hemorrhagic shock. Am. J. Physiol. **188** : 86, 1957.
41) Shoemaker, W. C., Walker, W. F. and Turk, L. N. III. : The role of the liver in the development of hemorrhagic ehock. Surg. Gyne. and Obst. **112** : 327, 1961.
42) Shorr, E., Zweifach, B. W. and Furchgott, R. F. : On the occurrence and site of vasotropic substance in traumatic shock. Science **102** : 489, 1945.
*43) Soejima, R., Tanaka, K., Tsushima, K., Ashizawa, K., Kawakami, Y., Saito, T., Nakamura, B., Mitsuhashi, M., Fujita, T., Narita, N., Sekino, E., Fukatsu, J. and Maeda, K. : Variation in the portal circulation after hepatectomy in dogs (Experimental study). J. J. S. S. **56** : 1088, 1956.
44) Thöle, F. : Chirurgie der Lebergeschwülste. Neue Deutsche Chirurgie Bd 7, Gustav Fischer, Jena. 1912.
*45) Uehara, Y. : Experimental studies on the hepatic circulation in the process of development of hemorrhagic shock into the irreversible phase and the concerned effect of artificial hibernation. J. J. S. S. **57** : 2030, 1957.
46) Wakin, K. G. and Gatch, W. D. : The effect of external temperature on shock. J. A. M. A. **121** : 903, 1943.
47) Wendel, W. : Über Leberlappen Resektion. Arch. klin. Chir. **119** : 982, 1920.
48) Wilkelmi, A. E. and Long, C. N. H. : Metabolic charges associated with hemorrhage. Ann. New York Acad. Sc. **49** : 605, 1948.
49) Wiggers, C. J. : Physiology of shock. Commonwealth Fund. New York, 1950,

(* in Japanese)

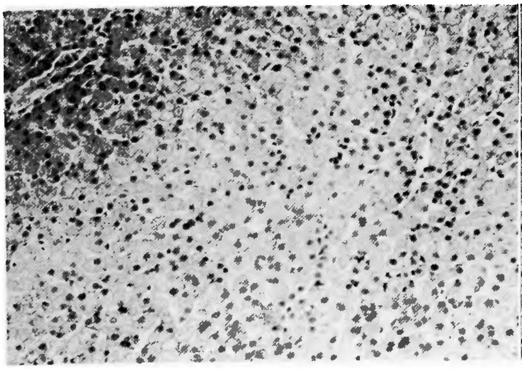


**Fig. 13** Before Bleeding Control
H. E. (×150)

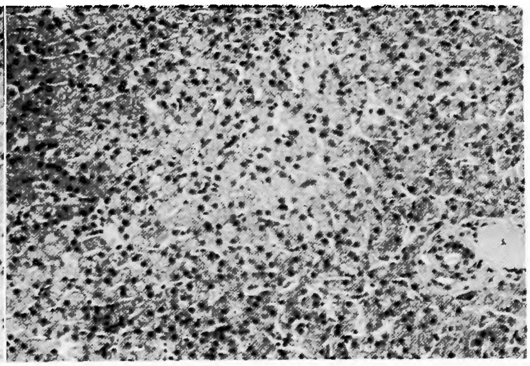


**Fig. 14** Before Bleeding Regenerated Liver
H. E. (×150)

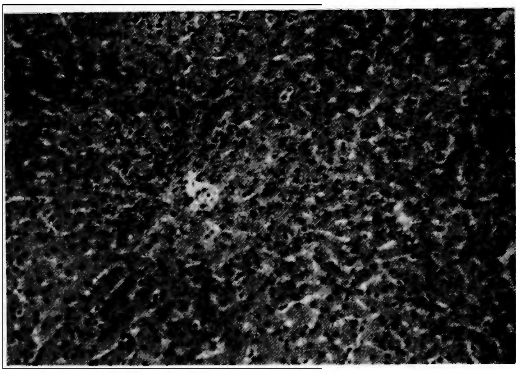


**Fig. 15** At the Time of Spont, Blood Return Control H. E. (×150)

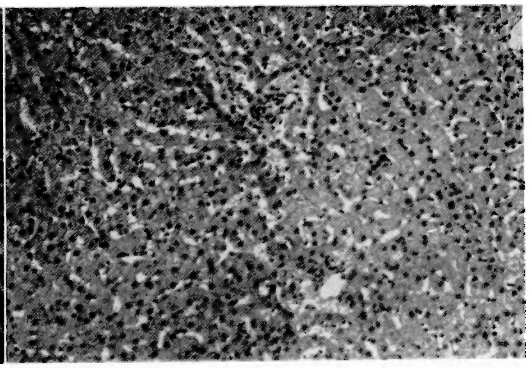


**Fig. 16** At the Time of Spont. Blood Return Regenerated Liver H. E. (×150)

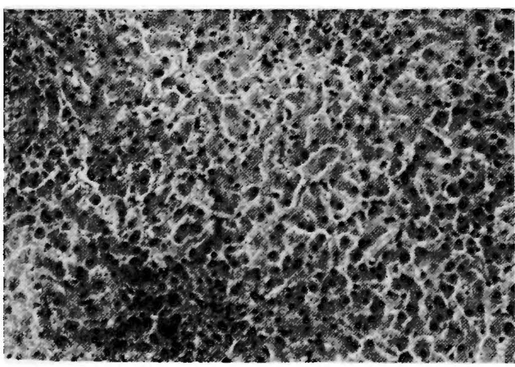


**Fig. 17** At the Time of 30% Spontaneous Blood Return Control H. E. (×150)

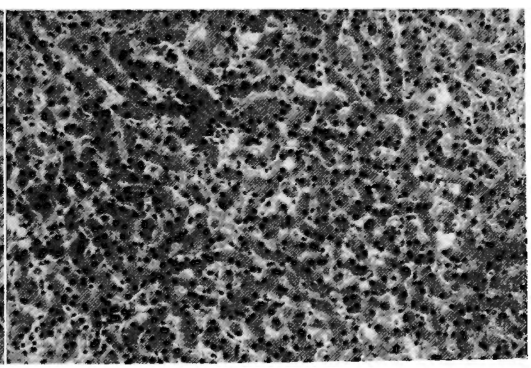


**Fig. 18** At the Time of 30% Spontaneous Blood Return Regenerated Liver H. E. (×150)

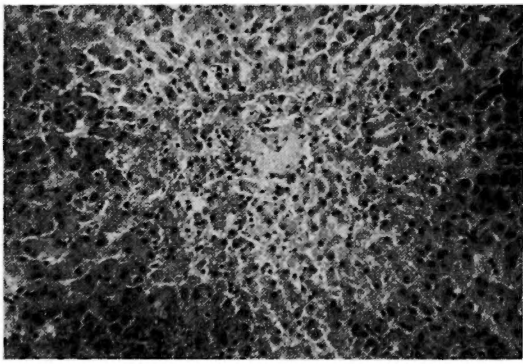


**Fig. 19** At the Time of 70% Spontaneous Blood Return Control H. E. (×150)

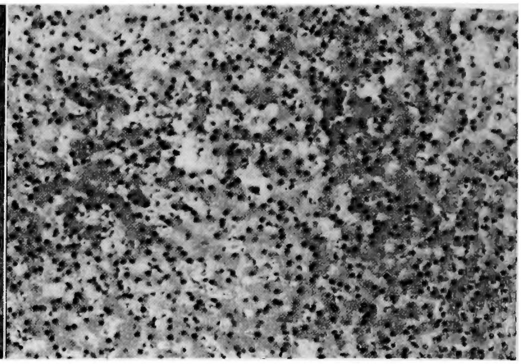


**Fig. 20** At the Time of 70% Spontaneous Blood Return Regenevated Liver H. E. (×150)

## 和文抄録

# 肝再生犬の出血ショックに対する態度

金沢大学医学部第2外科学教室(指導:本庄一夫教授)

辻 政彦

近年肝悪性腫瘍等に対し肝広汎切除が広く行なわれるようになるにつれ,再生肝の病態生理が臨床的にも一段と注目されるようになつた.肝切除後の残存肝は暫時高度の肝障害に陥るにもかかわらずよくそれに耐え著しい肝再生を行ない,その重量は急速に切除前値に接近する.

一方今日では生体に加えられる侵襲に対し肝が最も重要な役割を演ずる臓器の一つであることは,よく知られた事実である.されば肝障害に耐え著しい再生を行なつた再生肝は再び侵袭が加えられた場合,正常肝に比し抵抗性の亢進或いは減弱などの特異性を示すか,否かは興味ある問題である.かかる観点から50%肝切除により作成した肝再生犬及び正常犬を用い,著しい肝障害をもたらす出血ショックを Wiggers 法及び Lamson 変法により作成し,再生肝の病態生理の一面を窺わんと意図し次の様な結果を得た.

1) Wiggesr 法による出血ショックに於て,肝再生犬群,対照犬群の間に最大出血量,12時間及び24時間生存率に関して,何ら有意の差異を認めなかつた.

2) Lamson 変法による出血ショックに於て15%自然還血期返血を行なつた群では,対照群,肝再生犬群の何れも全て24時間以上生存し,30%自然還血期返血を行なつた群では,対照群,肝再生犬群の何れも全て24時間以内に死亡した.

3) Lamson 変法に於ける15%自然還血期返血群及び30%自然還血期返血群の何れに関しても,最大出血量,最大出血到達時間,自然還血開始時間,15%及び30%自然還血期到達時間,12時間及び24時間生存率に於て,気温,気候及び性別による影響を考慮しても,肝再生犬群と対照犬群との間に有意の差を見出すことが出来なかつた.即ち出血ショックの可逆相,不可逆相に於ける両群の態度には有意の差異を認めなかつた.

4) 門脈圧は肝再生犬群に於ては,出血前値に於ても,出血により下降した門脈圧の返血後回復率に於ても,対照群に比しやや高値を示し,門脈系血管抵抗のやや大なることを示唆した.

5) ヘマトクリット値の推移は肝再生犬群と対照群とはほぼ同様の傾向を示し有意の差異を認め得なかつた.

6) 以上により肝再生犬は出血ショックに対し正常犬と同様の態度を示し,正常犬に比し明らかにショック耐性を有するとは言えないまでも,決して劣るものではないと言える.